Section 7: Heart Failure in Patients With Left Ventricular Systolic Dysfunction

Overview

There are 3 primary issues that must be considered when treating heart failure (HF) patients with left ventricular (LV) systolic dysfunction: (1) improving symptoms and quality of life, (2) slowing the progression of cardiac and peripheral dysfunction, and (3) reducing mortality. General measures, such as salt restriction, weight loss, lipids control, and other nonpharmacologic measures are addressed in Section 6. Pharmacologic approaches to symptom control, including diuretics, vasodilators, intravenous inotropic drugs, anticoagulants, and antiplatelet agents are discussed at the end of this section.

Two classes of agents have become the recommended cornerstone of therapy to delay or halt progression of cardiac dysfunction and improve mortality: angiotensin-converting enzyme (ACE) inhibitors and β-blockers. Even while these agents are underused in the treatment of HF, new classes of agents have been added that show an impact on mortality, complicating decisions about optimal pharmacologic therapy. These include angiotensin receptor blockers (ARBs), aldosterone antagonists, and the combination of hydralazine and an oral nitrate, all of which are considered in the following recommendations.

ACE Inhibitors

Recommendation

7.1 ACE inhibitors are recommended for routine administration to symptomatic and asymptomatic patients with LVEF ≤40%. (Strength of Evidence = A) ACE inhibitors should be titrated to doses used in clinical trials, as tolerated during concomitant uptitration of β-blockers. (Strength of Evidence = C).

Background

There is compelling evidence that ACE inhibitors should be used to inhibit the renin-angiotensin system (RAS) in all HF patients with LV systolic dysfunction, whether or not they are symptomatic. A number of large clinical trials have demonstrated improvement in morbidity and mortality in HF patients with LV dysfunction, both chronically and post-MI.[1–3] The mortality benefit is strongest across New York Heart Association (NYHA) class II-IV HF, but appears present in patients who are NYHA class I as well.[4]

The major side effects of ACE inhibitors in patients with HF are hypotension and azotemia. Both are usually well tolerated and do not indicate the need to lower the dose or discontinue the ACE inhibitor. The azotemia commonly is related to the relative volume-depleted state caused by diuretic therapy. The major symptomatic side effect is a dry cough that usually does not require discontinuation of the drug. Care should be taken to distinguish between a cough that is ACE inhibitor–related and one that is due to worsening pulmonary congestion. If the cough impairs the patient's quality of life, alternative therapy, such as an ARB, may be considered.

Recommendation

7.2 It is recommended that other therapy be substituted for ACE inhibitors in the following circumstances:

- **In patients who cannot tolerate ACE inhibitors from cough, ARBs are recommended. (Strength of Evidence = A)**
  The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. (Strength of Evidence = C)
- **Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. (Strength of Evidence = C)**

Background

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Alternative trial prospectively tested the effect of an ARB in an ACE inhibitor intolerant population of patients with chronic HF and a LV ejection fraction (LVEF) <40%. The addition of candesartan in these patients resulted in a reduction in the composite endpoint of cardiovascular death or hospital admission for HF from 40% in the control group to 33% in the candesartan group over a mean follow-up of 34 months with a trend toward decreased all-cause mortality.[5] ARBs should be considered instead of ACE inhibitors primarily in patients who are intolerant of ACE inhibitors from intractable cough. ARBs appear as likely as ACE inhibitors to produce hypotension, worsening renal function, and hyperkalemia

See background to Recommendations 7.19–7.20 for information about isosorbide dinitrate/hydralazine.

β-Adrenergic Receptor Blockers

β-blocker therapy, advocated for HF by some investigators since the 1970s,[6] remains a major advance in the treatment of patients with LV systolic dysfunction. Several large-scale clinical trials, involving more than 10,000 patients, have provided unequivocal evidence of important reductions in both mortality and morbidity.[7,8] This class of

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drug is now established as routine therapy in patients with LV systolic dysfunction. This therapy is well tolerated by a large majority of patients with HF, even those with comorbid conditions like diabetes mellitus, chronic obstructive lung disease and peripheral vascular disease. A general summary of the recommendations for beta-blocker therapy is shown in Table 7.1.

Table 7.1. Summary of Recommendations for the Administration of β-Blocker Therapy*

General	Initiate at low doses Uptitrate gradually, generally no sooner than at 2-week intervals Use target doses shown to be effective in clinical trials Aim to achieve target dose in 8–12 weeks Maintain at maximum tolerated dose
Considerations if symptoms worsen or other side effects appear	Adjust dose of diuretic or other concomitant vasoactive medication Continue titration to target dose after symptoms return to baseline
Considerations if uptitration continues to be difficult	Prolong titration interval Reduce target dose Consider referral to a HF specialist
If an acute exacerbation of chronic HF occurs	Maintain therapy if possible Reduce dosage if necessary Avoid abrupt discontinuation If discontinued or reduced, reinstate gradually before discharge

*See Recommendations 7.3–7.9 for specific recommendations and conditions.

Recommendation

7.3 β-blockers shown to be effective in clinical trials of patients with HF are recommended for patients with an LVEF ≤40%. (Strength of Evidence = A)

Background

The marked beneficial effect of β-blockade on many clinical outcomes has been well demonstrated in large-scale clinical trials of symptomatic patients with NYHA class II–III HF (Table 4.7) using carvedilol, bisoprolol, or metoprolol controlled release/extended release (CR/XL).[9–11] These trials added β-blockade to background therapy that included ACE inhibitors and diuretics in more than 90% of patients. The trial results support benefit from both B_1 selective and nonselective β-blockers, whether ancillary properties are present or not. β-blocking agents with intrinsic sympathomimetic activity are likely to worsen survival and should be avoided in patients with HF.

Recommendation

7.4 The combination of a β-blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF ≤40%

- **Post-MI (Strength of Evidence = B)**
- **Non Post-MI (Strength of Evidence = C)**

Background

Randomized controlled data support the efficacy of ACE inhibitors in reducing both the likelihood of developing HF and the need for treatment or hospitalization in asymptomatic patients with an LVEF ≤35%.[12] Similar data are not available to support the use of β-blocker therapy in asymptomatic patients with systolic dysfunction. Nevertheless, a number of arguments support the routine use of β-blockade in these patients. Guidance is provided by studies indicating the effectiveness of β-blocker therapy in patients following MI with good symptomatic and functional recovery, yet residual ventricular systolic dysfunction. These studies enrolled a number of patients without clinical HF. Multiple studies suggest myocardial remodeling following β-blocker therapy in patients with symptomatic HF as well.

Recommendation

7.5 β-blocker therapy is recommended for patients with a recent decompensation of HF after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive agents, including inotropic support. Whenever possible, β-blocker therapy should be initiated in the hospital setting at a low dose prior to discharge in stable patients. (Strength of Evidence = B)

Background

Ongoing clinical experience and current trial data indicate that beginning β-blockade at low dose in the hospital is possible in patients with improved congestion and other symptoms.[13,14] Initiation of therapies in hospital is well known to result in better utilization and the attainment of more optimal doses of a variety of cardiovascular drugs.

β-blocker therapy should not be initiated in patients with acute decompensated heart failure (ADHF) with persistent symptoms and congestion. However, many patients hospitalized for HF are NYHA functional class IV from volume overload, and will improve sufficiently with standard therapy to allow introduction of β-blockade. The Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) provides strong evidence in a prospective, randomized trial that patients with advanced HF, treated aggressively to reduce congestion and improve symptoms, benefit substantially from the introduction of β-blockade.[15]

Recommendations

7.6 β-blocker therapy is recommended in the great majority of patients with LV systolic dysfunction, even if there is concomitant diabetes, chronic obstructive lung disease, or peripheral vascular disease.

β-blocker therapy should be used with caution in patients with diabetes with recurrent hypoglycemia, with asthma, or with resting limb ischemia. Considerable caution should be used if β-blockers are initiated in patients with marked bradycardia (<55 beats/min) or marked hypotension (systolic blood pressure <80 mm Hg). β-blockers are not recommended in patients with asthma with active bronchospasm. (Strength of Evidence = C)

7.7 It is recommended that β-blockade be initiated at low doses and uptitrated gradually, typically no sooner than at 2-week intervals. Doses found to be effective in HF trials are generally achieved in 8 to 12 weeks. Patients developing worsening HF symptoms or other side effects during titration may require a dosage adjustment of diuretic or concomitant vasoactive medications. If side effects resolve with medication adjustment, patients can subsequently be titrated to target or maximally tolerated doses. Some patients may require a more prolonged interval during uptitration, a temporary reduction in β-blocker dose, or, in rare cases, withdrawal of therapy. (Strength of Evidence = B)

7.8 It is recommended that β-blocker therapy be continued in most patients experiencing a symptomatic exacerbation of HF during chronic maintenance treatment. (Strength of Evidence = C)
A temporary reduction of dose in this setting may be considered. Abrupt discontinuation in patients with symptomatic exacerbation should be avoided. (Strength of Evidence = C)

If discontinued or reduced, β-blockers should be reinstated or the dose should be gradually increased before the patient is discharged.

Background

Clinical deterioration during stable maintenance therapy with β-blockers rarely is related to administration of these agents. Noncompliance with medications, progression of underlying LV dysfunction and the adverse influence of a number of comorbid factors, including the occurrence of ischemia, hemodynamic instability from arrhythmia, and pulmonary complications such as pneumonia, are much more likely to be responsible for clinical deterioration. The best course is to use standard therapy to relieve congestion and treat exacerbating factors, rather than reduce or discontinue β-blockade. A retrospective review of patients enrolled in the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial of patients hospitalized with ADHF, found that continuation of β-blockade did not interfere with symptomatic improvement during admission,[16] supporting the continuation of β-blockade in patients hospitalized with an episode of decompensation. This same observation was made in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial.[17]

Abrupt withdrawal of β-blockade should be avoided, especially in patients with coronary artery disease. Studies of the withdrawal of β-blockade in patients with persistent LV systolic dysfunction, but improved and stable clinical HF, have revealed a substantial risk of worsening HF and early death after β-blocker discontinuation.[18,19]

Recommendation

7.9 It is recommended that patients in whom difficulty is encountered in initiating, uptitrating or maintaining β-blocker therapy be referred to clinicians with special expertise in HF. (Strength of Evidence = B)

Background

In certain patients, frequent return visits for dose titration may be difficult to accommodate in a busy clinical practice. Trained personnel, including nurse practitioners, physician assistants, and pharmacists, with physician supervision, may more efficiently perform patient education and reevaluation during uptitration. HF specialty programs are more likely to have the resources to provide this follow-up and education.[20] Consultation or referral may be particularly beneficial when the clinical HF status of the patient is uncertain or problems arise during initiation of therapy or dose titration that may cause unwarranted discontinuation of therapy. Patients for β-blocker therapy should be compliant and have a good understanding of their disease and overall treatment plan. Patients should be aware that symptomatic deterioration is possible early in therapy and that symptomatic improvement may be delayed weeks to months.

Unresolved Issues

Implantation of Cardiac Pacemakers in Patients with Baseline Bradycardia. Given the strength of evidence supporting β-blocker therapy in patients with symptomatic HF, some physicians would consider pacemaker implantation when symptomatic bradycardia or heart block occurs during the initiation of this therapy. No data are available to support this practice. However, ventricular pacing alone may result in deterioration of ventricular function, negating any potential benefit from β-blockade.[21] Consideration should be given to the withdrawal of other drugs that may have bradycardic effects.

Angiotensin Receptor Blockers

Both ACE inhibitors and ARBs inhibit the renin-angiotensin-aldosterone system (RAAS), but by different mechanisms. ACE inhibitors block the enzyme responsible for converting angiotensin I to angiotensin II and for degrading various kinins. However, during chronic therapy, angiotensin II levels are not completely suppressed by ACE inhibitors for at least 2 reasons. Instituting an ACE inhibitor

increases renin levels, resulting in higher levels of angiotensin I, which will tend by mass action to produce greater angiotensin II levels. Production of angiotensin II may also occur through non-ACE enzyme systems not blocked by inhibitors of this enzyme.[22,23] Thus, despite treatment with ACE inhibitors in patients with chronic HF, angiotensin II levels may remain elevated and increase over time.[24,25]

ARBs block the effects of angiotensin II on the AT1 receptor, independent of the source of angiotensin II production. Coupled with angiotensin II "escape," this led to the hypothesis that ARBs might be superior to ACE inhibitors in HF and that the addition of ARBs to ACE inhibitors in patients with chronic HF might provide additional blockade of the RAAS and greater therapeutic benefit. The role of the kinin system as a mediator of the beneficial effects of ACE inhibitors in cardiovascular disease is becoming increasingly clear. ACE inhibitors reduce the degradation of kinins, which may lead to important therapeutic benefits not provided by ARBs, making the potential combination of the two agents more attractive.[26,27]

ACE inhibitors can have some troublesome side effects, including cough and angioedema, which may limit therapy with these agents. ARBs have been demonstrated to be well tolerated in randomized trials of patients judged to be intolerant of ACE inhibitors by their clinicians, although these primarily reflect intolerance from cough, skin rashes, and angioedema. Both drugs have similar effects on blood pressure, renal function, and potassium.

Recommendation

7.10 ARBs are recommended for routine administration to symptomatic and asymptomatic patients with an LVEF ≤40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency. (Strength of Evidence = A)

Background

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Alternative trial prospectively tested the effect of an ARB in an ACE inhibitor intolerant population of patients with chronic HF and an LVEF <40%. The addition of candesartan in these patients resulted in a reduction in the composite endpoint of cardiovascular death or hospital admission for HF from 40% in the control group to 33% in the candesartan group over a mean follow-up of 34 months with a trend toward decreased all-cause mortality.[5] Post-hoc subgroup analysis of a small subgroup of patients in the Valsartan in Heart Failure Trial (Val-HeFT) also found that patients intolerant to ACE inhibitors had fewer HF hospitalizations and a trend toward improved mortality with the addition of valsartan.[28] These data suggest that an ARB should be used in ACE inhibitor intolerant patients with chronic HF and LVEF <40%. ARBs should be titrated as tolerated, in conjunction with β-blocker therapy, to target doses used in clinical trials. ARBs should be considered instead of ACE inhibitors primarily in patients who are intolerant of ACE inhibitors because of intractable cough. ARBs appear as likely as ACE inhibitors to produce hypotension, worsening renal function, and hyperkalemia.

Recommendation

7.11 Individual ARBs may be considered as initial therapy rather than ACE inhibitors for patients with the following conditions:

- **HF Post-MI (Strength of Evidence = A)**
- **Chronic HF and systolic dysfunction (Strength of Evidence = B)**

Background

Support for the use of the ARB, valsartan, in patients post-MI is provided by The Valsartan in Acute Myocardial Infarction Trial (VALIANT), which randomized 14,703 patients 0.5 to 10 days post-MI to valsartan, valsartan plus captopril, or captopril alone. Patients enrolled had clinical or radiologic signs of HF, evidence of LV systolic dysfunction, or both.[29] The primary end point was all-cause mortality. There were no statistical differences among the 3 groups at a mean follow-up of 24.7 months. With monotherapy, hypotension and renal dysfunction were more common in the valsartan group, and cough, rash, and taste disturbance were more common in the captopril group. The authors concluded that monotherapy with valsartan was equivalent to monotherapy with captopril. OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) randomized 5477 patient with heart failure or LV dysfunction post-MI to captopril or losartan.[30] The primary endpoint was all-cause mortality. There were 946 deaths during a mean follow-up of 2.7 years: 499 (18%) in the losartan group and 447 (16%) in the captopril group (relative risk 1.13 [95% CI 0.99–1.28], $P = .07$). Thus valsartan appears equivalent to captopril in patients with HF or LV dysfunction post-MI. The data do not clearly support equivalence of losartan to captopril in these patients.

In patients with chronic HF and LV dysfunction, 2 recent reviews have addressed the equivalence of ARBs and ACE inhibitors.[31,32] One meta-analysis concluded that ARBs should be considered "suitable alternatives" to ACE inhibitors. CMS (Centers for Medicare and Medicaid Services) has used this review to consider both ARBs and ACE inhibitors as acceptable to satisfy performance standards in patients with HF.[33] A second review suggested that ACE-inhibitors remain first line therapy, whereas ARBs were recommended for ACE-intolerant patients.[32]

Recommendation

7.12 ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that

angioedema has been reported infrequently with these agents. (Strength of Evidence = B)

The combination of hydralazine and oral nitrates may be considered in this setting in patients who do not tolerate ARB therapy. (Strength of Evidence = C)

Background

Angioedema and ARBs. Nearly three-quarters of patients in CHARM-Alternative were intolerant to ACE inhibitors because of hypotension, 13% from hyperkalemia, 11% from renal dysfunction, and 4% from angioedema/anaphylaxis.[5] In that study, 3 patients taking candesartan and none taking placebo had angioedema. None of the episodes were life-threatening and only 1 of the 3 patients discontinued candesartan. The 3 cases of angioedema all occurred in the 39 patients intolerant to ACE inhibitors because of angioedema. Thus the risk of recurrent angioedema with ARBs in patients with angioedema from ACE inhibition appears to be acceptable, assuming careful instructions and patient monitoring.

7.13 The routine administration of an ARB is not recommended in addition to ACE inhibitor and β-blocker therapy in patients with a recent acute MI and LV dysfunction. (Strength of Evidence = A)

Background

Post-MI Studies. The VALIANT trial evaluated the clinical effectiveness of ACE inhibitors and ARBs in patients with a recent MI (0.5–14 days), an LVEF ≤40% and clinical or radiographic signs of HF.[30] The addition of valsartan to captopril did not result in a significant improvement in total mortality or cardiovascular mortality compared to captopril alone, and there were more drug-related adverse events in the valsartan-captopril group.

The Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) was designed to prove that losartan would be superior or not inferior to captopril in decreasing all-cause mortality in patients with MI complicated by LV systolic dysfunction.[31] There was a trend toward decreased all-cause mortality in the captopril group compared with losartan, and fewer captopril-treated patients experienced sudden death or a resuscitated cardiac arrest.[31] The addition of losartan to captopril did not result in a significant improvement in total mortality or cardiovascular mortality compared with captopril alone, and there were more drug-related adverse events in the losartan-captopril group.

The results of VALIANT cannot be directly compared with those of Val-HeFT and CHARM, because VALIANT was conducted in patients with recent MI and both an ACE inhibitor and ARB were added, rather than adding the ARB to a stable patient on chronic ACE inhibitor therapy. These data suggest that an ARB may be beneficial when added to an ACE inhibitor and β-blocker in patients with chronic HF, but not in those with HF because of a recent MI.

Aldosterone Antagonists

Sustained activation of aldosterone appears to play an important role in the pathophysiology of HF.[34,35] Increased renin and angiotensin II levels contribute to the stimulation of aldosterone secretion. Elevated circulating levels of this hormone enhance sodium retention and potassium and magnesium loss. Aldosterone upsets autonomic balance by increasing sympathetic activation and parasympathetic inhibition and promotes cardiac and vascular structural remodeling through collagen synthesis.[36–38]

Although ACE inhibition may transiently decrease aldosterone secretion, there are diverse stimuli other than angiotensin II for the production of this hormone.[39] Studies suggest a rapid return of aldosterone to levels similar to those before ACE inhibition.[40] ARBs have not been frequently used in patients with HF because of concerns about side effects and hyperkalemia in the presence of ACE inhibitors. However, the potential pathophysiologic role of aldosterone and a pilot study that suggested low doses of spironolactone seemed to be tolerated in HF, led to additional investigation of these agents in severe heart failure and subsequently in post-MI heart failure.[41]

Recommendations

7.14 Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from LV systolic dysfunction (LVEF ≤35%) while receiving standard therapy, including diuretics. (Strength of Evidence = A)

7.15 Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical HF signs and symptoms and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a beta blocker. (Strength of Evidence = A)

7.16 Aldosterone antagonists are not recommended when creatinine is >2.5 mg/dL (or creatinine clearance is <30 ml/min) or serum potassium is >5.0 mmol/L or in conjunction with other potassium-sparing diuretics. (Strength of Evidence = A)

7.17 It is recommended that serum potassium concentration be monitored frequently following initiation or change in an aldosterone antagonist. Monitoring should reflect protocols followed in clinical trials. (Strength of Evidence = A)

7.18 In the absence of persistent hypokalemia (<4.0 mmol/L), supplemental potassium is not recommended in patients taking an aldosterone antagonist. (Strength of Evidence = A)

Background

The Randomized Aldactone Evaluation Study (RALES) was designed to determine the effect of low-dose spironolactone on survival in severely symptomatic (recent or current NYHA class IV) HF patients treated with an ACE inhibitor, loop diuretic, and, in many cases, digoxin.[42] The study enrolled a total of 1663 patients with severe LV systolic dysfunction (LVEF ≤35%) resulting from ischemic and nonischemic etiologies. All-cause mortality was the prespecified primary endpoint. There were 386 (46%) deaths in the placebo group compared with 284 (35%) in the spironolactone group. The risks of sudden death or of death from progressive HF were both reduced. The frequency of hospitalization for HF was 35% lower in patients treated with spironolactone compared with placebo. Greater improvement was noted in NYHA functional class in those receiving spironolactone. Because deaths in class III patients were designated as a worsening in NYHA class, this functional improvement likely reflects the mortality benefit of the drug.

The inclusion and exclusion criteria for the RALES trial are important to consider when applying the study results to clinical practice. The yearly mortality rate in the placebo group was high, reflecting the advanced HF of study participants. The potential benefit of aldosterone antagonists in patients with milder HF and lower risk cannot be determined from RALES data. Patients with potassium levels >5.0 mmol/L were excluded, as were patients with abnormal renal function, defined as a creatinine >2.5 mg/dL. Patients recruited into the trial met the potassium inclusion criteria despite the frequent concomitant use of potassium supplementation at baseline (28%). Adhering to these patient characteristics may be necessary to avoid excessive hyperkalemia during spironolactone treatment. It should be noted that only 10% of placebo and 11% of spironolactone patients in the RALES trial were treated with β-blocker therapy.

Spironolactone should be used in conjunction with standard therapy, including ACE inhibitors, digoxin, diuretics, and β-blockers. It should be initiated at a dose of 12.5 to 25 mg per day. Spironolactone can be titrated to 37.5 mg or 50 mg with careful monitoring in patients with refractory heart failure or persistent hypokalemia. Serum potassium and creatinine should be monitored closely in the first few weeks of therapy. If the serum potassium exceeds 5.0 mmol/L, then the dose of spironolactone should be decreased to 25 mg every other day and medications that could contribute to hyperkalemia should be adjusted. The risk of hyperkalemia with aldosterone antagonism is increased in patients with older age, diabetes, higher serum creatinine levels, and higher ACE inhibitor doses. In community settings the risk is far higher than documented during careful monitoring in trial settings, and may be as high as 20%.[43] This risk should be taken into careful consideration when treating with an aldosterone antagonist, and remains present even after successful initiation of this therapy. Patients should continue to be monitored carefully and should be instructed not to take the aldosterone antagonist during any circumstances of volume loss such as gastroenteritis.

In addition to hyperkalemia, gynecomastia or breast pain may be important side effects. They were reported in 10% of the men randomized to spironolactone versus 1% of the males in the placebo group in the RALES trial. These side effects were more frequent in patients taking digoxin.

Clinical studies with the selective aldosterone antagonist, eplerenone, have demonstrated favorable results in patients with HF after acute MI. A multicenter, randomized, double-blind, placebo-controlled trial, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), tested the effect of eplerenone versus placebo in 6642 patients.[44] Patients were enrolled after an acute MI if they had an LVEF ≤40% and HF documented by signs and symptoms. HF signs and symptoms were not required if patients had diabetes. Exclusion criteria for the study included creatinine >2.5 mg/dL and serum potassium >5.0 mmol/L. Patients were generally receiving agents shown to be effective in reducing risk in patients after acute MI, including β-blockers, ACE inhibitors, aspirin and cholesterol-lowering agents. The hypothesis was that eplerenone would reduce overall mortality and cardiovascular mortality or hospitalization.

The results, after an average follow-up 16 months, revealed a statistically significant reduction in cardiovascular mortality or hospitalization and all-cause mortality and hospitalization in the group receiving eplerenone. There was also a significant reduction in sudden cardiac death favoring eplerenone treatment.

Adverse reactions to eplerenone were uncommon. As with spironolactone, serious hyperkalemia was more prevalent with eplerenone treatment. It should be noted that baseline serum potassium concentration in both the eplerenone and placebo groups was 4.3 mmol/L. As outlined in the recommendation for use, it is important to monitor electrolytes, especially potassium. Post-hoc analyses suggested that patients who were not on ACE inhibitors or ARBS and β-blockers had less benefit from the addition of eplerenone than those on these neurohormonal antagonists.

Remodeling Post MI. Another study randomized 134 patients postanterior MI after revascularization to spironolactone versus placebo.[45] All patients were on ACE inhibitors. After 1 month, EF was improved, end-diastolic dimension was reduced, and markers of collagen synthesis were reduced in the spironolactone group, indicating an improvement in LV remodeling after MI. One of the limitations of this study was that only 31% of patients were on β-blockers.

Aldosterone Antagonists in Mild to Moderate HF. Patients enrolled in RALES had chronic severe HF (NYHA IV at enrollment or in the past). EPHESUS studied patients who were post-MI. Aldosterone antagonists have not been proven effective in patients with mild to moderate HF in

the absence of recent MI or in patients with HF and preserved LV systolic function.

Selective Versus Nonselective Aldosterone Antagonists. The efficacy of selective and nonselective aldosterone antagonists is generally considered to be equivalent. The potential advantage of a selective aldosterone blocker that blocks the only the mineralocorticoid receptor over is a reduction in side effects. A nonselective blocker, such as spironolactone, blocks the mineralocorticoid, glucocorticoid, androgen, and progesterone receptors, resulting in potential gynecomastia and sexual dysfunction.

Hyperkalemia. Hyperkalemia is a life-threatening complication of aldosterone antagonists and is much more likely to occur in patients with diabetes or renal insufficiency or in those taking ACE inhibitors or ARBs. When more than one of these risk factors is present, the likelihood of hyperkalemia increases. In RALES and EPHESUS, aldosterone antagonists were not initiated if the creatinine was >2.5 g/dL or serum potassium was >5.0 mmol/L. In RALES, the potassium was monitored every 4 weeks for 12 weeks, every 3 months up to a year, and every 6 months after the first year. In the EPHESUS trial, in which patients were taking a larger number of concomitant medications, potassium was measured at 48 hours, at 4–5 weeks, and then every 3 months. Potasssium was measured 1 week after a dose increase of an aldosterone antagonist. Although patients with creatinine <2.5 mg/dL were enrolled in the clinical trials, very few patients actually had a creatinine >1.7 mg/dL. Thus additional monitoring should be considered in these patients.

Few patients will tolerate an aldosterone antagonist in the absence of concomitant therapy with a potassium-wasting diuretic. Potassium supplements and potassium-containing salt supplements should be reduced or, if possible, discontinued. Serum potassium monitoring should be at least as rigorous as in RALES and EPHESUS and more rigorous in patients with multiple risk factors. Nonsteroidal antiinflammatory agents, including COX-2 inhibitors, should be avoided because they may worsen renal insufficiency, increasing the risk of hyperkalemia.

Oral Nitrates and Hydralazine

Recommendations

7.19 A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE inhibitors for African Americans with LV systolic dysfunction.
- **NYHA III or IV HF (Strength of Evidence = A)**
- **NYHA II HF (Strength of Evidence = B) (See Section 15—Special Populations)**

7.20 A combination of hydralazine and isosorbide dinitrate may be considered in non–African-American patients with LV systolic dysfunction who remain symptomatic despite optimized standard therapy. (Strength of Evidence = C)

Background

The Vasodilator Heart Failure Trial (V-HeFT) was the first major randomized heart failure trial and was conducted in Veterans Administration hospitals throughout the US. Patients who remained symptomatic with mild to severe symptoms of HF despite treatment with diuretics and digoxin were randomized to a combination of hydralazine and isosorbide dinitrate or prazosin or placebo. The combination of hydralazine and isosorbide dinitrate was associated with a reduction in all-cause mortality compared to both placebo and prazosin that was of borderline statistical significance ($P = .053$).[46] In V-HeFT II, the combination of hydralazine and isosorbide dinitrate was compared with enalapril in a population similar to V-HeFT I.[47] All-cause mortality was 28% lower with enalapril than with the hydralazine isosorbide dinitrate combination. However, quality of life and peak exercise capacity as measured by peak oxygen consumption were better with hydralazine-isosorbide dinitrate.

The African-American Heart Failure Trial (A-HeFT) enrolled 1050 self-identified African-American patients who had New York Heart Association class III or IV HF with dilated ventricles and systolic dysfunction.[48] In this placebo-controlled, blinded, and randomized trial, subjects were randomly assigned to receive a fixed combination of isosorbide dinitrate plus hydralazine or placebo in addition to standard therapy for HF. The primary end point was a composite score made up of weighted values for death from any cause, a first hospitalization for HF, and change in the quality of life. The study was terminated early because of a significantly higher mortality rate in the placebo group than in the group given the fixed combination of isosorbide dinitrate plus hydralazine (10.2% vs 6.2%, $P = .02$). The mean primary composite score was significantly better in the group given isosorbide dinitrate plus hydralazine than in the placebo group, as were its individual components: 43% reduction in the rate of death from any cause, 33% relative reduction in the rate of first hospitalization for HF, and an improvement in the quality of life. These results taken together constitute a strong recommendation for the addition of the fixed combination of isosorbide dinitrate/hydralazine to the standard medical regimen for HF in African Americans. Data cannot exclude a benefit of the isosorbide dinitrate/hydralazine combination in non–African Americans when added to the standard medical regimen for HF.

Polypharmacy

Recommendation

7.21 Additional pharmacologic therapy should be considered in patients with HF due to systolic dysfunction who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and β-blocker. The choice of specific agent will be influenced by clinical considerations, including renal function status,

chronic serum potassium concentration, blood pressure, and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. (Strength of Evidence = C)

- **Addition of an ARB. (Strength of Evidence = A)**
- **Addition of an aldosterone antagonist:**
  - **for severe HF (Strength of Evidence =A)**
  - **for moderate HF (Strength of Evidence = C)**
- **Addition of the combination of hydralazine/isosorbide dinitrate:**
  - **for African Americans (Strength of Evidence = A)**
  - **for others (Strength of Evidence = C)**

7.22 Additional pharmacological therapy should be considered in patients with HF due to systolic dysfunction *who are unable to tolerate a β blocker* and have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended due to the high risk of hyperkalemia. (Strength of Evidence = C)

- **Addition of an ARB. (Strength of Evidence = C)**
- **Addition of an aldosterone antagonist:**
  - **for severe HF (Strength of Evidence = C)**
  - **for moderate HF (Strength of Evidence = C)**
- **Addition of the combination of hydralazine/isosorbide dinitrate:**
  - **for African Americans (Strength of Evidence = C)**
  - **for others (Strength of Evidence = C)**

Background

Polypharmacy is required for optimal management to slow progression and improve outcome in patients with LV systolic dysfunction. An ACE inhibitor plus a β-blocker is standard background therapy. An ARB can be substituted for an ACE inhibitor if indicated or desired. An ARB can be added to an ACE inhibitor in individuals in whom β-blocker is contraindicated or not tolerated. The optimal choice of additional drug therapy to further improve outcome in patients already treated with 2 of these 3 drugs is not firmly established. An aldosterone inhibitor, an ARB (if the patient is already on an ACE inhibitor) and the combination isosorbide dinitrate of and hydralazine have all been shown to exert further benefit in controlled trials, but have not been the subject of comparative trials. The choice among these agents may be influenced by the patient's age, renal function, serum potassium, racial background, and severity of the clinical syndrome. Certain combinations would require careful monitoring. For example, if an ARB or aldosterone antagonist were combined with an ACE inhibitor, with or without β-blocker therapy, elderly patients would require close monitoring, especially those with diabetes or renal insufficiency.

The use of 4 or more of these drugs in combination cannot be recommended on the basis of clinical trial evidence for additional efficacy, but such combinations have been used in clinical trials without apparent adverse effects. In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Added trial an ARB was safely administered to patients receiving an ACE inhibitor, β-blocker and aldosterone inhibitor.[49] In the A-HeFT study, black patients were given isosorbide dinitrate-hydralazine in addition to an ACE inhibitor, an ARB, and an aldosterone inhibitor with no apparent adverse effect.[48] Nonetheless, the use of combinations of 4 or more of these drugs would not be based on evidence for further efficacy and should mandate close monitoring of blood pressure, renal function, and serum potassium.

As discussed previously in this section, ARBs, aldosterone antagonists, and hydralazine/isosorbide dinitrate all have been shown to be beneficial in patients with chronic HF with or without beta blocker therapy. However, no study has specifically evaluated patients who are intolerant to beta blockers. Those who are intolerant due to hypotension or worsening HF are likely to have more severe HF and to be at higher risk of hypotension, worsening renal function, or hypokalemia with additional medical therapy. Thus closer clinical and laboratory monitoring is important.

Diuretic Therapy

Loop and distal tubular diuretics are necessary adjuncts in the medical therapy for HF when symptoms are the result of sodium and water retention. Diuretics reduce congestive symptoms and signs and can be titrated as needed to restore euvolemia and to reach an estimated ''dry'' weight goal for the patient.

Relief of signs and symptoms must be achieved without causing side effects, particularly symptomatic hypotension or worsening renal function. Underutilization of diuretic therapy is common, but excessive diuresis is also problematic, limiting ventricular preload and producing excessive lowering of blood pressure, especially in conjunction with antihypertensive drugs such as ACE inhibitors, ARBs, and β-blockers. Diuretic administration should be accompanied by a recommendation for dietary sodium restriction to between 2000 and 3000 mg daily for the typical patient with HF (see Section 6). Fluid restriction is best reserved for the patient refractory to diuretics with a high oral fluid intake or symptomatic hyponatremia.

Although some physicians express concern about the long-term safety of diuretics, this concern is not supported by any controlled data. There are few controlled studies of

diuretics because few symptomatic patients can be managed without them. Still, there are data to support the safety and efficacy of diuretics.[50] A trial in which patients with stable and relatively mild HF without evidence of significant volume overload were randomized to substitution of an ACE inhibitor or continued diuretic showed that the large majority of patients required reinstatement of diuretic therapy.[51] Very small trials suggest that in patients with LV dysfunction with or without HF, ACE inhibitor therapy may prevent remodeling more than diuretics, but that diuretics may be superior for symptom improvement.[52,53] However, there are no controlled clinical trial data prospectively evaluating the overall impact of diuretic therapy on mortality in patients with HF. Diuretics may cause activation of the RAAS, potentiate hypotensive effects of ACE inhibitors, and may decrease cardiac output, especially in patients with diastolic LV dysfunction. Diuretics also may induce hypokalemia and hypomagnesemia.

Recommendation

7.23 Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms (orthopnea, edema, and shortness of breath), or signs of elevated filling pressures (jugular venous distention, peripheral edema, pulsatile hepatomegaly, and, less commonly, rales). (Strength of Evidence = A)
Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with HF. (Strength of Evidence = B)

Background

Loop Diuretics. Loop diuretics, which act on the ascending limb of the renal medullary loop of Henle, are considered the diuretic class of choice for the treatment of HF. These drugs produce a greater fractional excretion of filtered sodium than is induced by thiazide-type diuretics. The onset of action with intravenous administration is within minutes, making this route of administration preferable for the acutely symptomatic or hospitalized patient (see Section 12).

Thiazide Diuretics. Thiazide diuretics, which inhibit sodium reabsorption in the distal renal tubule, may be effective as monotherapy in HF patients with mild volume overload and preserved renal function. They are generally superior to loop diuretics as antihypertensive agents. They are delivered to their site of action by filtration and are ineffective when the glomerular filtration rate falls below 30 mL/min.

Potassium-Sparing Diuretics. Potassium-sparing diuretics, other than aldosterone antagonists, have no direct diuretic activity. Several are formulated in combination with thiazides for the treatment of hypertension, but are not generally useful in HF. For patients with excessive potassium losses on loop diuretics, coincident administration of these agents can be helpful. However, because of their beneficial effects on prognosis and ability to facilitate diuresis, aldosterone antagonists are preferred for this purpose. The use of these agents for purposes other than as a diuretic is discussed earlier in this section.

Tables 7.2 and 7.3 provide dosage and other information about loop diuretics, thiazides, and potassium-sparing diuretics.[54–57]

Table 7.2. Loop Diuretics

Agent	Initial Daily Dose (mg)	Maximum Total Daily Dose (mg)	Elimination	Duration of Action (hr)
Furosemide*	20–40 mg qd or bid	600 mg	65%R 35%M	4–6
Bumetanide*	0.5–1.0 mg qd or bid	10 mg	62%R 38%M	6–8
Torsemide*	10–20mg qd	200 mg	20%R 80%M	12–16
Ethacrynic acid*,+	25–50 mg qd or bid	200 mg	67%R 33%M	6

Adapted from references 56–59.
Equivalent doses: furosemide 40 mg = bumetanide 1 mg = torsemide 20 mg = ethacrynic acid 50 mg.
R = renal; M = metabolic; B= excreted into bile; U = unknown.
*Available for oral or intravenous administration (no dosage adjustments).
+Non-sulfa containing, may be used in sulfa-allergic patients.

Recommendation

7.24 The initial dose of diuretic may be increased as necessary to relieve congestion. Restoration of normal volume status may require multiple adjustments over many days and occasionally weeks in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with short-acting loop diuretics, increasing administration frequency to twice or even 3 times per day will provide more diuresis with less physiologic perturbation than larger single doses. (Strength of Evidence = B)
Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present, particularly those with right-sided HF and refractory fluid retention despite high doses of other loop diuretics. (Strength of Evidence = C)

Intravenous administration of diuretics may be necessary to relieve congestion. (Strength of Evidence = A)

Diuretic refractoriness may represent patient noncompliance, a direct effect of diuretic use on the kidney, or progression of underlying cardiac dysfunction.

Table 7.3. Other Diuretics

Agent	Initial Daily Dose (mg)	Maximum Total Daily Dose (mg)	Elimination	Duration of Action (hr)
Thiazides				
Chlorothiazide*	250–500 qd or bid	1000 mg	R	6–12
Chlorthalidone	12.5–25 mg qd	100 mg	65%R 10%B 25%U	24–72
Hydrochlorothiazide	25 mg qd or bid	200 mg	R	6–12
Metolazone	2.5 mg qd	20 mg	80%R 10%B 10%U	12–24
Idapamide	2.5 mg qd	5 mg	M	36
*May be given IV in doses of 250–1000 mg.				
Potassium-Sparing				
Spironolactone*	12.5–25 qd	50 mg*	M	48–72
Eplerenone*,+	25–50 qd	100 mg*	R, M	
Amiloride	5 qd	20 mg	R	24
Triamterene	50–75 bid	200 mg	M	7–9

R = renal; M = metabolic; B= excreted into bile; U = unknown.
References, HF in Patients with LV Dysfunction
*Higher doses have been used to control volume retention or hyperkalemia but close monitoring is mandatory.
+Do not use if creatinine clearance is ≤30 mL/min or with cytochrome 3A4 inhibitors.

Background

HF can adversely affect the pharmacokinetics of diuretics in a number of ways. Delayed absorption, resulting from gut edema from high central venous pressure, can reduce peak serum concentration. The volume of distribution is variable in the setting of chronic HF. Relative hypotension or reduced cardiac output producing a limitation in renal blood flow reduces the delivery of diuretic to the kidney. In general, these limitations can be overcome by successively increasing the dose administered.

Recommendation

7.25 Addition of chlorothiazides or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high-dose loop diuretic therapy. But chronic daily use, especially of metolazone, should be avoided if possible because of the potential for electrolyte shifts and volume depletion. These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer-acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used. (Strength of Evidence = C)

Background

Thiazide-type diuretics can be used in combination with loop diuretics to augment natriuresis when high doses of loop diuretic are ineffective at restoring euvolemia. Improved natriuresis from the combination of these 2 classes of diuretics is expected as they act at different sites in the kidney to produce sodium loss. In addition, resistance to loop diuretics can occur, partially due to progressive hypertrophy of distal renal tubular endothelial cells. This results in greater distal tubular reabsorption of sodium, which in turn reduces the net natriuretic effect of loop diuretics. Combining a thiazide-type diuretic with a loop diuretic typically will overcome this compensatory hypertrophy and result in a significantly greater diuretic effect.

Recommendation

7.26 Careful observation for the development of side effects, including electrolyte abnormalities, symptomatic hypotension, and renal dysfunction, is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = B)

Background

Hypokalemia from excessive potassium wasting is common during loop diuretic therapy, especially during the reversal of significant volume overload. Thiazide-type diuretics also produce potassium wasting. Serum potassium concentration should be monitored when diuretics are used, particularly during initiation and uptitration of this therapy, with supplements given as needed.

Excessive diuresis may lead to volume depletion during treatment. Symptoms may include fatigue and shortness of breath, rather than the more predictable symptoms of dizziness. Hyperkalemia may accompany mild volume depletion and is more likely to occur in patients receiving ACE inhibitors and aldosterone blockers, especially in patients with diabetes.

Use of loop and distal tubular diuretics in combination may be necessary to relieve symptoms, but may result in excessive volume loss and electrolyte disturbance. Distal

tubular diuretics should be introduced cautiously when they are combined with loop diuretics, and patients should be monitored closely for side effects. Initially, only single low doses (eg, metolazone 2.5 mg) should be administered to determine the magnitude of response. If necessary, higher doses may be used subsequently. Twice-daily dosing of distal agents is generally not helpful because they have a long duration of action. In most cases, the frequency of use can be cut back to every other day or as needed based on a weight threshold.

Worsening renal function is common with excessive diuresis, especially when patients are receiving ACE inhibitors or ARBs. Fortunately, reduction in diuretic dose and restoration of euvolemia will return renal function to baseline levels in almost all cases unless hypovolemia has been prolonged. Intensification of diuretic therapy in these patients may be accompanied by a worsening of renal function reflected by modest elevations in blood urea nitrogen and serum creatinine concentration. Some reduction in renal function may be a necessary tradeoff for symptom relief in this setting.

The occurrence of reduced renal function should prompt a review of the patient's current medications to avoid concomitant administration of nephrotoxic drugs or drugs that reversibly affect renal function (eg, nonsteroidal anti-inflammatory drugs) and to determine if dose reduction in medications dependent on renal clearance (eg, digoxin) is warranted. It is essential to recognize progressive renal insufficiency from decreasing renal perfusion that will require adjustment of diuretic therapy.

Loop diuretics may be associated with a variety of other side effects that may require additional treatment to correct. Rapid intravenous administration of high-dose loop diuretics should be avoided whenever possible, because hearing loss to the point of deafness can result from middle ear toxicity. Skin reactions from photosensitivity to rashes are not uncommon, and other hypersensitivity reactions including interstitial nephritis may occur. High doses of loop diuretics can worsen glucose tolerance and may result in hyperuricemia and symptoms of gout, prompted by increased uric acid reabsorption. Thiazide diuretics share most of the side effects seen with loop diuretics, although an association with pancreatitis appears be unique to loop diuretics.

Recommendation

7.27 Patients requiring diuretic therapy to treat fluid retention associated with HF generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or even discontinuing diuretics may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention. (Strength of Evidence = C)

Background

Reduced diuretic requirement is not uncommon during the course of HF treatment. The initiation of more effective therapies, such as ACE inhibitors and β-blockers, may result in substantial improvement in underlying LV dysfunction and in neurohormonal abnormalities that result in sodium and water retention. Improvement in dietary sodium compliance is not unusual during chronic therapy for HF and may substantially reduce the need for diuretic therapy. Reevaluation of diuretic dose and frequency should occur over the course of initiation and titration of therapy.

Recommendation

7.28 It is recommended that patients and caregivers be given education that will enable them to demonstrate understanding of the early signs of fluid retention and the plan for initial therapy. (Strength of Evidence = C)

Selected patients may be educated to adjust daily dose of diuretic in response to weight gain from fluid overload (typically short-term weight gain of 2 to 4 lb). (Strength of Evidence = C)

Background

Episodic increases in sodium intake over weeks and months of follow-up are expected, given the natural variation in diet common in the daily lives of patients with HF. If untreated, this excessive dietary sodium intake may result in development or recurrence of congestive symptoms. The ability to recognize early signs and symptoms of volume overload is an important aspect of self-care for these patients. Intervention early in the development of fluid overload may allow restoration of volume status without hospitalization.

A strategy effective in many patients involves adjustment of the diuretic dose according to increases in daily weight. Some patients find it effective to increase diuretic empirically when dietary sodium indiscretion occurs. In some patients with advanced HF, monitoring of renal function and potassium is necessary before or during these periods.

Digoxin

Although little controversy exists as to the benefit of digoxin in patients with symptomatic LV systolic dysfunction and concomitant atrial fibrillation, the debate continues over its current role in similar patients with normal sinus rhythm. Information regarding digoxin's mechanism of action and ongoing analyses of clinical data from the Digitalis Investigation Group (DIG) trial and the combined databases of several other large trials provide evidence of digoxin's

efficacy.[58–64] Digoxin, a drug that is inexpensive and can be given once daily, represents the only oral agent with positive inotropic effects approved for the management of HF.[65] Used in combination with other standard therapy, digoxin has an important therapeutic role in symptomatic patients with HF from reduced LVEF.

The efficacy of digoxin in HF from systolic dysfunction has traditionally been attributed to its relatively weak positive inotropic action arising from inhibition of sodium-potassium ATPase and the resulting increase in cardiac myocyte intracellular calcium. However, digitalis has additional actions that may contribute significantly to its beneficial effects in patients with HF. Digoxin has important neurohormonal modulating effects that cannot be ascribed to its inotropic action, and it ameliorates autonomic dysfunction as shown by studies of heart rate variability, which indicate increased parasympathetic and baroreceptor sensitivity during therapy.[66–68]

Recommendation

7.29 Digoxin should be considered for patients with LV systolic dysfunction (LVEF ≤40) who have signs or symptoms of HF while receiving standard therapy, including ACE inhibitors and β-blockers:
- **NYHA class II-III (Strength of Evidence = A)**
- **NYHA class IV (Strength of Evidence = B)**

Background

The DIG trial provides important data concerning the efficacy of digoxin in patients with HF from reduced EF.[58] In the main part of this trial, 6800 patients with LVEF ≤45% were randomized to digoxin or placebo in addition to diuretics and ACE inhibitors. The primary end point of all-cause mortality was not significantly different between the placebo and the digoxin groups. The need for hospitalization and cointervention (defined as increasing the dose of diuretics and ACE inhibitors or adding new therapies for worsening HF) was significantly lower in the digoxin group, even in those patients who were not previously taking digoxin. Twenty-eight percent fewer patients on digoxin compared with placebo were hospitalized for worsening HF.

Results from the DIG study showed a neutral effect on the primary study endpoint, mortality from any cause, during an average follow-up of approximately 3 years. This differs from other oral agents with inotropic properties, which have been associated with an adverse effect on mortality. These long-term data are consistent with recent results obtained from an analysis of the combined PROVED and RADIANCE databases.[61] In this analysis, patients who continued digoxin as part of triple therapy with diuretics and an ACE inhibitor were much less likely to develop worsening HF (4.7%) than those treated with a diuretic alone (39%, $P < .001$), diuretic plus digoxin (19%, $P = .009$), or diuretic plus an ACE inhibitor (25%, $P = .001$).

Although the number of patients in the DIG trial with NYHA functional class IV HF was limited, retrospective analysis of this subgroup found clear evidence of clinical benefit of digoxin.[69] Other results from this trial confirm that digoxin works across the spectrum of LV systolic dysfunction. A prespecified subgroup analysis of patients with evidence of severe HF, as manifested by LVEF <25% or cardiothoracic ratio (CTR) >0.55, showed the benefit of digoxin.[66,70] The following reductions in the combined endpoint of all-cause mortality or hospitalization were seen on digoxin compared with placebo: 16% reduction (95% CI 7–24%) in patients with an LVEF <25%, and a 15% reduction (95% CI 6–23%) in patients with a CTR >0.55.[70] Reductions in the risk of the combined endpoint of HF-related mortality or hospitalization were even more striking: 39% for patients with LVEF <25% and 35% for patients with a CTR >0.55.

Evidence for the efficacy of digoxin in patients with mild symptoms of HF has been provided by a second retrospective cohort analysis of the combined PROVED and RADIANCE databases.[71] The outcome of patients in these trials randomized to digoxin withdrawal or continuation was categorized using a prospectively obtained HF score based on clinical signs and symptoms. Patients in the mild HF group who were randomized to digoxin withdrawal were at increased risk of treatment failure and had deterioration of exercise capacity and LVEF compared with patients who continued digoxin (all $P < .01$).

Recommendation

7.30 It is recommended that the dose of digoxin, which should be based on lean body mass, renal function, and concomitant medications, should be 0.125 mg daily in the majority of patients and the serum digoxin level should be <1.0 ng/mL. (Strength of Evidence = C)

Background

Recent data suggest that the target dose (and serum concentration) of digoxin therapy should be lower than traditionally assumed. Although higher doses may be necessary for maximal hemodynamic effects,[64] beneficial neurohormonal and functional effects appear to be achieved at relatively low serum digoxin concentrations (SDC) typically associated with daily doses of 0.125 to 0.25 mg.[64,72,73] A retrospective analysis of the relationship of serum digoxin concentration to outcomes in the DIG trial demonstrated a strong direct relationship between the risk of death and serum digoxin concentration, with concentrations >1.2 ng/mL being associated with harm, whereas concentrations <1.0 ng/mL were associated with favorable outcomes.[74] These findings supporting the efficacy of low SDC are reinforced by a retrospective cohort analysis of the combined PROVED and RADIANCE databases indicating that patients with a low SDC (<0.9 ng/mL) were no more likely to experience worsening symptoms of HF on maintenance

digoxin than those with a moderate (0.9–1.2 ng/mL) or high (>1.2 ng/mL) SDC.[74,75] All SDC groups were significantly less likely to deteriorate during follow-up compared with patients withdrawn from digoxin.

Therefore, patients with LV systolic dysfunction and normal sinus rhythm should be started on a maintenance dose of digoxin (no loading dose) of 0.125 or 0.25 mg once daily based on ideal body weight, age, and renal function For patients with normal renal function, a dose of 0.25 mg/day will be typical. Many patients with HF have reduced renal function and should begin at 0.125 mg daily. Patients with a baseline conduction abnormality, or who are small in stature or elderly, should be started at 0.125 mg/day, which can be up-titrated if necessary. After dosing has continued for a sufficient period for serum concentration to reach steady state (typically 2 to 3 weeks), some clinicians consider the measurement of a SDC, especially in elderly patients or those with impaired renal function where the digoxin dose often is not predictive of SDC. SDC measurements may be considered when (1) a significant change in renal function occurs; (2) a potentially interacting drug (amiodarone, quinidine, verapamil, itraconazole, erythromycin, clarithromycin, ritonavir, propafenone, or cyclosporine, and others) is added or discontinued; or (3) confirmation of suspected digoxin toxicity is necessary in a patient with signs/symptoms or ECG changes consistent with this diagnosis. Samples for trough SDC should be drawn more than 6 hours after dosing; otherwise, the result is difficult to interpret because the drug may not be fully distributed into tissues.

Recommendation

7.31 Adequate control of the ventricular response to atrial fibrillation in patients with HF is recommended. (Level of Evidence = B)

7.32 High doses of digoxin (maintenance dose >0.25 mg daily) for the purpose of rate control are not recommended. (Strength of Evidence = C)

Background

Digoxin alone is often inadequate to control ventricular response in patients with atrial fibrillation. Digoxin slows ventricular response to atrial fibrillation through enhancement of vagal tone. However, with exertion or other increases in sympathetic activity, vagal tone may diminish and ventricular rate accelerate. Addition of a β-blocker complements the pharmacologic action of digoxin and provides more optimal rate control. For patients with a contraindication to β-blockers, amiodarone is a reasonable alternative, although chronic amiodarone use is associated with both thyroid disease and lung toxicity. If amiodarone is added, the dose of digoxin should be reduced and the SDC should be monitored to maintain the serum concentration in the desired range. Some clinicians advocate the short-term, intravenous administration of diltiazem for the acute treatment of patients with very rapid ventricular response, especially those with hemodynamic compromise. In the acute and chronic treatment of atrial fibrillation with rapid ventricular response the clinician must consider the benefits of rate control versus the negative inotropic effects of the agent.

Although digoxin continues to play a role in some patients with HF and atrial fibrillation, the traditional practice of arbitrarily increasing the dose and SDC of digoxin until ventricular response is controlled should be abandoned, because the risk of digoxin toxicity increases as well.

AV node ablation is a consideration in patients who remain symptomatic with atrial fibrillation despite adequate rate control or in those who cannot tolerate drug therapy for rate control. Although there are studies that determine adequate rate control in atrial fibrillation, the recommendations followed in the Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management (AFFIRM) trial are a reasonable starting point.[76] These recommendations include: a resting heart rate ≤80 bpm, an average heart rate by Holter monitor of ≤100 bpm, and no heart rate >110% of the age-predicated maximum or a heart rate ≤110 bpm in a 6-minute walk test.

Anticoagulation and Antiplatelet Drugs

Patients with HF are recognized to be at increased risk for arterial or venous thromboembolic events. In addition to atrial fibrillation and poor ventricular function, which promote stasis and increase the risk of thrombus formation, patients with HF have other manifestations of hypercoagulability. Evidence of heightened platelet activation, increased plasma and blood viscosity, and increased plasma levels of fibrinopeptide A, β-thromboglobulin, D-dimer, and von Willebrand factor have been found in many patients.[77–79] Despite a predisposition, estimates regarding the incidence of thromboemboli in patients with HF vary substantially between 1.4% and 4.2% per 100 patient years.[80–82] Although variability in the reported incidence likely results from differences in the populations studied and the methodology used to identify these events, the consensus is that pulmonary and systemic emboli are not common in HF patients in sinus rhythm. Traditionally, discussion of anticoagulation in patients with HF has centered on warfarin. Antiplatelet agents are often used in patients with HF from ischemic heart disease.

Previous guidelines have recommended warfarin anticoagulation in patients with HF complicated by atrial fibrillation or prior thromboembolic events.[83,84] Warfarin anticoagulation was specifically not recommended in patients with HF in the absence of these indications. There have been no randomized, controlled trials of warfarin in patients with HF. Recommendations regarding its use, in the absence of atrial fibrillation or clinically overt systemic or pulmonary thromboemboli, must be made on the basis of cohort data and expert opinion. The likely incidence of thromboembolic events and the possibility of averting them with warfarin are important considerations for any guideline recommendation. In addition, the potential beneficial effects of warfarin on coronary thrombotic events,

independent of embolic phenomena, must be taken into account. The substantial clinical trial data reflecting the beneficial effects of antiplatelet therapy in patients with ischemic heart disease suggest that the role of this therapy in patients with LV dysfunction should be addressed.

Recommendation

7.33 Treatment with warfarin (goal INR 2.0–3.0) is recommended for all patients with HF and chronic or documented paroxysmal atrial fibrillation (Strength of Evidence = A) or a history of systemic or pulmonary emboli, including stroke or transient ischemic attack (Strength of Evidence = C), unless contraindicated.

Background

Previous guideline recommendations have been positive concerning warfarin therapy in patients with HF complicated by atrial fibrillation, a common clinical presentation. The benefit of warfarin anticoagulation in this setting is well established through several randomized trials.[85] Warfarin anticoagulation should be implemented in these patients unless clear contraindications exist.

Recommendation

7.34 It is recommended that patients with symptomatic or asymptomatic ischemic cardiomyopathy and documented recent large anterior MI or recent MI with documented LV thrombus be treated with warfarin (goal INR 2.0–3.0) for the initial 3 months post-MI (Strength of Evidence B) unless contraindicated.

Other patients with ischemic or nonischemic cardiomyopathy and LV thrombus should be considered for chronic anticoagulation, depending on the characteristics of the thrombus, such as its size, mobility, and degree of calcification. (Strength of Evidence = C)

Background

LV thrombus is a frequent finding in patients with dilated dysfunctional ventricles, especially in patients who have suffered a large anterior MI, although the incidence appears to be declining with modern therapies.[86–88] LV thrombus is associated with thromboembolism, especially cerebral embolism.[89–91] Two-thirds of these embolic events occur in the first week after MI.[89,90] When LV mural thrombus is present, anticoagulation does appear to reduce the incidence of subsequent embolic events.[91] There are no randomized trials of anticoagulation for LV thrombus, but the data presented have led to a recommendation for short-term (3 months) anticoagulation in patients with a large anterior MI and wall motion abnormality or in patients with LV thrombus.[92]

Recommendation

7.35 In the absence of the indications included in Recommendations 33 and 34, warfarin anticoagulation may be considered in patients with dilated cardiomyopathy and LVEF ≤35%. Careful assessment of the potential risks and benefits should be undertaken in individual patients. (Strength of Evidence C)

Background

Cohort analyses examining the relationship between warfarin use and noncoronary thromboembolism in patients with HF have not yielded consistently positive findings.[80,82,93–96] It is possible that the lack of consistent benefit was related to the low incidence of identifiable embolic events in these populations. Other retrospective evaluations of the use of anticoagulation in patients with HF have yielded conflicting results.[2,9,97–99] A recent review suggested that anticoagulation with warfarin in patients with HF reduced death and cardiovascular events but that the data were insufficient to recommend routine use.[100] Two prospective randomized trials of anticoagulation have been published since that review but both were underpowered. The Warfarin/Aspirin Study in Heart Failure (WASH) randomized 279 patients with HF to warfarin (INR target 2.5), 300 mg aspirin, or no treatment.[101] There were no differences in the combined primary outcomes of death, MI, or stroke. However, significantly more patients randomized to aspirin were hospitalized for ADHF or serious adverse gastrointestinal events. In the larger WATCH (Warfarin and Antiplatelet Therapy in Heart Failure Trial) 1587 outpatients with LVEF <35% were randomized to warfarin (INR target 2.5), 162 mg aspirin, or 75 mg clopidogrel.[102] Once again there were no differences in the primary endpoint of death, MI, or stroke. However, as in WASH, more patients randomized to aspirin were hospitalized for HF. A recent retrospective analysis of 290 patients with heart failure and EF <35% and idiopathic dilated cardiomyopathy reported an odds ratio of 3.4 (P = .027) for stroke in those with LV thrombus but no difference in mortality.[103] In the absence of strong data the decision to anticoagulate must be an individual one.

A recent cohort analysis of the SOLVD population focused on the relation between warfarin use and the risk of all-cause mortality rather than risk for embolic events.[104] After adjustment for baseline differences, patients treated with warfarin at baseline had a 24% lower risk of mortality during follow-up. Warfarin use also was associated with an 18% reduction in the combined endpoint of death or hospitalization for HF. In the SOLVD population, the benefit associated with warfarin use was not significantly influenced by (1) presence or absence of symptoms, (2) randomization to enalapril or placebo, (3) gender, (4) presence or absence of atrial fibrillation, (5) age, (6) EF, (7) NYHA class, or (8) etiology.

The benefit associated with warfarin use in the cohort analysis of the SOLVD population was related to a reduction in cardiac mortality. Specifically, there was a significant reduction among warfarin users in deaths that were identified as sudden, in deaths associated with HF, and in fatal MI. There was no significant difference in deaths considered cardiovascular but non-cardiac, including pulmonary embolism and fatal stroke. Some caution is needed related to this finding as the number of cardiovascular deaths that were non-cardiac was far smaller than the number of cardiac deaths.

Reduction in ischemic events is 1 potential explanation for the apparent benefit from warfarin in the SOLVD study. Warfarin users showed a reduced rate of hospitalization for unstable angina or nonfatal MI. Prior investigations in patients following acute MI showed that warfarin anticoagulation, when begun within 4 weeks, reduced the incidence of fatal and non-fatal coronary events, as well as pulmonary emboli and strokes.[101]

As with other post-hoc cohort analyses, it is possible that the findings from the SOLVD study may result from unidentified differences between the treatment groups, for which statistical correction could not adequately adjust. For this reason, evidence from any cohort study must be considered less powerful than that derived from randomized, controlled trials. Nevertheless, in the absence of randomized data, the SOLVD cohort analysis represents reasonable evidence to support more aggressive use of warfarin anticoagulation in patients with reduced LVEF and sinus rhythm than has previously been recommended. Because this analysis does not identify the ideal warfarin dose in this patient population, dosing should likely conform to that derived from prior randomized trials performed in patients without mechanical prosthetic valves (ie, INR 2.0–3.0).

Recommendations

7.36 Long-term treatment with an antithrombotic agent is recommended for patients with HF due to ischemic cardiomyopathy, whether or not they are receiving ACE inhibitors. (Strength of Evidence = B)

Aspirin is recommended in most patients for whom anticoagulation is not specifically indicated because of its proven efficacy in non-HF patients with ischemic heart disease, its convenience, and lower cost. Lower doses of aspirin (75 or 81 mg) may be preferable. (Strength of Evidence = C)

Warfarin (goal INR 2.0–3.5) and clopidogrel (75 mg) also have prevented vascular events in post-MI patients and may be considered as alternatives to aspirin. (Strength of Evidence = B)

7.37 Routine use of aspirin is not recommended in patients with HF not from ischemic cardiomyopathy and without other evidence of atherosclerotic vascular disease. (Strength of Evidence = C)

7.38 Aspirin and an ACE inhibitor in combination may be considered for patients with HF where an indication for both drugs exists. (Strength of Evidence = C)

Generally the lowest effective aspirin dose (75 or 81 mg/day) should be administered in this setting. (Strength of Evidence = C)

Background

Combined Use of Aspirin and an ACE Inhibitor. Strong evidence supports the clinical benefit of both aspirin and ACE inhibitors in ischemic heart disease and atherosclerosis.[105–108] However, post-hoc analyses of large randomized trials involving ACE inhibitors in HF and post-MI have raised the possibility of an adverse drug interaction between ASA and ACE inhibitors.[109–111]

It is critical to understand the possible nature of the adverse interaction raised by these retrospective analyses. Because both aspirin and ACE inhibitors are beneficial in ischemic heart disease, patients taking both agents might be expected to do better than patients on either agent alone. However, if the 2 drugs have similar mechanisms of action, then additive benefit would not be expected. Another possibility is that one drug might antagonize the effects of the other, resulting in reduced benefit from the combination.

Post-MI. Early work concerning the nature of the interaction in ischemic heart disease, using data from CONSENSUS II and GUSTO-1 in post-MI patients, suggested not only lack of additive benefit, but also the possibility of a negative effect on mortality from the combination of ASA and ACE inhibition. A large-scale meta-analysis of patients after acute MI failed to confirm an adverse interaction, with evidence of significant benefit from ACE inhibition in patients taking and not taking aspirin.[112] However, the point estimate for the reduction in mortality in patients taking the combination of ASA and ACE inhibition, whereas not statistically less than for ASA alone, was lower, providing no support for additive benefit from the 2 drugs.

Heart Failure. A retrospective cohort analysis of the SOLVD study found that patients on antiplatelet therapy (assumed to be ASA in the great majority of cases) derived no additional survival benefit from the addition of enalapril. On the other hand, there is no clear evidence of harm from the combination of ASA and ACE inhibitors in patients with HF.[109]

Relationship to Dose. There is also some evidence that the potential interaction between ASA and ACE inhibitor may be dose-related. A recent meta-analysis of all hypertension and HF patients who have received both ASA and ACE inhibitors suggests that ASA at doses $\leq$100 mg did

not interact with ACE inhibitors.[113] Any interaction, if observed, occurred at higher doses of aspirin.

A potential mechanism for the hypothesized adverse interaction between ASA and ACE inhibitors in patients with HF involves prostaglandin synthesis. ACE inhibition is felt to augment bradykinin, which in turn stimulates the synthesis of various prostaglandins that may contribute vasodilatory and other salutary effects. In the presence of ASA, the bradykinin-induced increase in prostaglandins should be attenuated or blocked, potentially reducing the benefits of ACE inhibition. Invasive hemodynamic monitoring has demonstrated that the acute hemodynamic effect of enalapril is blunted by concomitant administration of aspirin.[114] Another possibility is that ASA and ACE inhibitors act in a similar fashion in HF so that no added benefit is gained from the combination. ACE inhibitors appear to reduce ischemic events in HF patients possibly through antithrombotic effects, which could mimic those of antiplatelet agents. Recent study results suggesting that ASA may have independent beneficial action on ventricular remodeling support the hypothesis of similar mechanisms of action for ACE inhibitors and ASA.[115]

Development of the ADP antagonists, ticlopidine and clopidogrel, provide alternative therapy for platelet inhibition that does not appear to influence prostaglandin synthesis.[116] In direct comparison with aspirin, large-scale clinical trial results have established the efficacy of clopidogrel in the prevention of vascular events in patients with arteriosclerotic disease.[117] Clinical data are limited with ADP antagonists in HF. However, hemodynamic evaluation found a similar reduction in systemic vascular resistance in HF patients treated with the combination of ACE inhibitor and ticlopidine versus ACE inhibitor alone, suggesting no adverse hemodynamic interaction between ACE inhibition and this type of antiplatelet compound.[118] Definitive resolution of the therapeutic implications of the ASA–ACE inhibitor interaction and determination of alternative therapy, if any, in HF awaits the results of additional studies.

Amiodarone Therapy

Ventricular arrhythmias are common in HF patients, and sudden cardiac death continues to account for a significant proportion of the mortality in this syndrome. Sudden death in HF may arise from a variety of causes, including bradyarrhythmias, conduction disturbances, electromechanical dissociation, acute MI, or pulmonary embolus. However, the majority of these deaths are thought to be due to ventricular tachyarrhythmias. Therefore, there has been considerable interest in the potential role of antiarrhythmic drug therapy in patients with HF.[119]

Despite the obvious clinical need, antiarrhythmic drug therapy remains ineffective at reducing mortality in patients with HF. After disappointing findings with d-sotalol and dofetilide, interest remained strong in the potential ability of amiodarone, another class III agent, to reduce sudden death and improve mortality in patients with HF and LV systolic dysfunction. However, results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) do not support the use of this drug to reduce mortality in patients with HF.[119]

There are justifiable concerns about antiarrhythmic therapy in patients with HF. Patients with HF are at higher risk for proarrhythmic effects of antiarrhythmic agents. This has been demonstrated with class Ia (quinidine, procainamide), class Ic, and class III (dofetilide) agents. Virtually all antiarrhythmic agents have been shown to have adverse hemodynamic effects sufficient to have negative consequences in patients with HF.

Despite the ability of Vaughn Williams class Ia (quinidine and procainamide) and Ic (flecainide and encainide) drugs to suppress ventricular ectopy and nonsustained ventricular tachycardia in patients with HF, these agents have been shown to substantially increase the risk of serious arrhythmia and premature death in other cardiovascular diseases.[85,94] Pure class III agents (d-sotalol, d,l-sotalol, and dofetilide) also reduce the frequency of serious ventricular arrhythmia in HF, but randomized trials suggest either increased risk or no benefit from these agents. In the SWORD Trial, d-sotalol produced a significant increase in total and cardiac mortality rates in post-MI patients.[95] Results of the DIAMOND-CHF Trial demonstrated that dofetilide, while reducing the risk of hospitalization for HF, had no effect on all-cause mortality.[96] A significant incidence of torsade de points was noted, despite the exclusion of patients with prolongation of the QT interval at baseline.

Recommendation

7.39 Antiarrhythmic agents, including amiodarone, are not recommended for the primary prevention of sudden death in patients with HF. (Strength of Evidence = A).

Background

The results of the SCD-HeFT failed to demonstrate a favorable effect of amiodarone therapy on mortality in patients with HF from reduced LVEF.This prospective, controlled trial tested the hypothesis that either amiodarone or an ICD, or both, improve survival compared with placebo in patients with HF. The study enrolled 2521 patients with NYHA II or III HF of ischemic or nonischemic etiology and an LVEF $<35\%$ and randomly assigned them to implantable cardioverter defibrillator (ICD), amiodarone, or placebo. The patients were well treated: 87% were on ACE inhibitors or ARBs and 78% were on β-blockers at last follow-up. The trial found no evidence for a benefit of amiodarone compared with placebo on all-cause mortality, but did demonstrate a favorable effect for ICD placement (Section 9).

Results of 2 smaller trials appear to support the SCD-HeFT findings.[104,120] One double-blind, randomized, placebo-controlled trial enrolled 674 patients with a mean age of 66 years. The majority (56%) had NYHA class II

symptoms, and their mean LVEF = 26%. No differences were observed in all-cause or cardiac mortality or sudden death rates between the amiodarone and placebo groups. The other study did suggest a beneficial effect of amiodarone, but there were significant limitations in the design and conduct of this trial. Treatment assignment was randomized, but not double-blind or placebo-controlled. The trial was discontinued prematurely when a 28% reduction was observed in all-cause mortality, the primary endpoint. Although not strictly involving HF patients, 2 post-MI trials using amiodarone also found no effect of this drug on all-cause mortality.[105,108]

Recommendations

7.40 In patients with HF and an ICD, amiodarone may be considered to reduce the frequency of repetitive discharges. (Strength of Evidence = C)

7.41 It is recommended that patients taking amiodarone therapy and digoxin or warfarin generally have their maintenance doses of many commonly used agents, such as digoxin, warfarin, and statins, reduced when amiodarone is initiated and then carefully monitored for the possibility of adverse drug interactions. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended. (Strength of Evidence = A)

Background

Amiodarone therapy modifies the pharmacokinetics of a number of drugs commonly used in patients with HF. In particular, it may substantially enhance the actions of digoxin and warfarin, with the definite potential of adverse clinical consequences. In general, the digoxin dose should be reduced by half, but follow-up determination of SDC is desirable to ensure a concentration of 0.5–0.9 ng/mL. The warfarin dose should be adjusted to maintain the INR target for the individual patient.

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